313

Yamanishi T[1], Chapple C[2], Chess-Williams R[2], Yasuda K [1], Sakakibara R[3], Uchiyama T[3], Yoshida K[1]
1. Dokkyo University, 2. Sheffield University, 3. Chiba University

THE ROLE OF BETA3-ADRENOCEPTOR SUBTYPES IN MEDIATING RELAXATION OF THE PIG URETHRAL SMOOTH MUSCLE

Aims of Study

Beta3-adrenoceptors are predominantly present in the bladder and urethra (1). Beta 3-adrenoceptors have been reported to predominantly mediate relaxation of bladder detrusor smooth muscle (2). However it has not been reported which beta-adrenoceptor subtypes mediate relaxation of the urethra. This study investigates the role of beta-adrenoceptor subtypes in mediating relaxation of the pig urethra in vitro.

Methods

Circular strips of urethral smooth muscle of the pig were isolated, and the mucosa and serosa removed. Tissues were precontracted with 50mM KCl, and beta-adrenoceptor agonists (isoprenaline, salbutamol or BRL 37344) were added cumulatively, and concentration-relaxation curves (CRCs) were obtained. CRCs to agonists were obtained in the absence and presence of antagonists and antagonist affinity values were calculated.

Results

Isoprenaline (non-selective beta-agonist, n=30) and BRL37344 (beta3-adrenoceptor agonist, n=4) relaxed KCl precontracted muscle strips with high potency (pEC_{50}=7.2 and 8.1, respectively), whilst salbutamol (beta2-adrenoceptor agonist) had low potency(pEC_{50}=6.1). Mean % maximal relaxation responses of BRL37344 and salbutamol relative to the 30µM isoprenaline maximum relaxation were 89.8% and 76.7 %.

Propranolol (10-100nM) antagonized CRCs to isoprenaline with a high affinity (apparent pK_B=8.6), but the Schild plot had a slope significantly ($p<0.01$) less than unity (0.68), suggesting that responses were mediated by more than one beta-adrenoceptor subtype. CGP20712A (beta1-antagonist, 10-30µM) had no effects on responses to isoprenaline, indicating beta1-adrenoceptors did not participate in the response. The affinity of ICI118551 (beta2-antagonist) for antagonism of responses to isoprenaline was high (apparent pK_B =8.03), but the Schild slopes were significantly ($p<0.01$) less than unity (0.79) suggesting that responses were mediated by more than one receptor. SR59230A (beta3-antagonist) antagonized CRCs to isoprenaline with a relatively high affinity (apparent pK_B=7.4), and with a Schild slope significantly ($p<0.01$) less than unity (0.62), indicating that responses may be mediated by more than one beta-adrenoceptor subtype. In contrast to that observed with isoprenaline, ICI118551 competitively antagonized (Schild plot of unity) responses to salbutamol with a high affinity (pA2=8.5). SR59230A (10nM-100nM) antagonized CRCs to BRL37344 without affecting maximum responses with apparent pK_B values of 7.72±0.11 but the Schild plots had slopes less than unity (0.85±0.20) suggesting that responses were mediated by more than one receptor.

TABLE –Effects of beta-adrenoceptor antagonists on concentration-relaxation responses to beta-agonists in pig urethral smooth muscle

Agonist	Antagonist	Concentration	pA2 (PKB)*	Schild slope
Isoprenaline	propranolol	10-100nM	8.55±0.06	0.68±.006**
	CGP20712A	10-30µM	No effect	
	ICI118551	30-300nM	8.03±0.52	0.79±0.37**
	SR59230A	10-100nM	7.38±0.07	0.62±0.02**
Salbutamol	ICI118551	3-30nM	8.50±0.12	1.03±0.08
BRL37344	SR59230A	10-100nM	7.72±0.11	0.85±0.2

*Apparent pKB values were calculated when slope of the Schild plot was different from unity
**Schild plot was significantly ($p<0.05$) different from unity

Conclusions

Our data in vitro suggest that beta3-adrenoceptor predominantly mediated responses, with β_2-adrenoceptor also had a contribution to relaxation of the urethral smooth muscle of the female pig.

References

J Urol 2002.168:2706-2710.
Br J Pharmacol 2002.